Docket No.: BPI-187

Application No.: 10/622932

In the claims:

Please amend claims 2, 3, and 15 as follows:

1. **(Original)** A method of treating a TNFα-related disorder in a subject, wherein the TNFα-related disorder is selected from the group consisting of a spondyloarthropathy, a pulmonary disorder, a coronary disorder, a metabolic disorder, anemia, pain, a hepatic disorder, a skin disorder, a nail disorder, or vasculitis, comprising administering to the subject a therapeutically effective amount of a neutralizing, high affinity TNFα antibody, such that said TNFα-related disorder is treated.

2. **(Currently amended)** A method of treating a TNFα-related disorder in a subject, wherein the TNFα-related disorder is selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis, comprising administering to the subject a therapeutically effective amount of a neutralizing, high affinity anti-TNFα antibody, such that said TNFα-related disorder is treated.

3. **(Currently amended)** A method of treating a TNFα-related disorder in a subject, wherein the TNFα-related disorder is selected from the group consisting of age-related cachexia, Alzheimer's disease, brain edema, inflammatory brain injury, chronic fatigue syndrome, dermatomyositis, drug reactions, edema in and/or around the spinal cord, familial periodic fevers, Felty's syndrome, fibrosis, glomerulonephritides (e.g. post-streptococcal glomerulonephritis or IgA nephropathy), loosening of prostheses, microscopic polyangiitis, mixed connective tissue disorder, multiple myeloma, cancer and cachexia, multiple organ disorder, myelo dysplastic syndrome, orchitism osteolysis, pancreatitis, including acute, chronic, and pancreatic abscess, periodontal disease polymyositis, progressive renal failure, pseudogout, pyoderma gangrenosum, relapsing polychondritis, rheumatic heart disease, sarcoidosis, sclerosing cholangitis, stroke, thoracoabdominal aortic aneurysm repair (TAAA), TNF receptor

associated periodic syndrome (TRAPS), symptoms related to Yellow Fever vaccination, inflammatory diseases associated with the ear, chronic ear inflammation, or pediatric ear inflammation. ~~In still another embodiment of the invention, the TNFα-related disorder is a~~ Crohn's disease-related disorder, juvenile arthritis/Still's disease (JRA), uveitis, sciatica, prostatitis, endometriosis, choroidal neovascularization, lupus, Sjogren's syndrome, and wet macular degeneration, comprising administering to the subject a therapeutically effective amount of a neutralizing, high affinity anti-TNFα antibody, such that said TNFα-related disorder is treated.

4. **(Original)** The method of any one of claims 1, 2, or 3, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a $K_d$ of $1 \times 10^{-8}$ M or less and a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of $1 \times 10^{-7}$ M or less.

5. **(Original)** The method of any one of claims 1, 2, or 3, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof with the following characteristics:

a) dissociates from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

6. **(Original)** The method of any one of claims 1, 2, or 3, wherein the antibody is an isolated human antibody, or an antigen-binding portion thereof, with a light chain variable

region (LCVR) comprising the amino acid sequence of SEQ ID NO:1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

7. **(Original)** The method of any one of claims 1, 2, or 3, wherein the antibody is D2E7.

8. **(Original)** A method of treating a subject suffering from a TNFα-related disorder, wherein the TNFα-related disorder is selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis, comprising administering a therapeutically effective amount of a TNFα antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNFα with a $K_d$ of $1 \times 10^{-8}$ M or less and a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of $1 \times 10^{-7}$ M or less, such that said TNFα-related disorder is treated.

9. **(Original)** A method of treating a subject suffering from a TNFα-related disorder, wherein the TNFα-related disorder is selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis, comprising administering a therapeutically effective amount a TNFα antibody, or an antigen-binding fragment thereof, with the following characteristics:

a) dissociates from human TNFα with a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, such that said TNFα-related disorder is treated.

10. **(Original)** A method of treating a subject suffering from a TNFα-related disorder selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis, comprising administering a therapeutically effective amount a TNFα antibody, or an antigen-binding fragment thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, such that said TNFα-related disorder is treated.

11. **(Original)** The method of any one of claims 8, 9, or 10, wherein the TNFα antibody, or antigen binding fragment thereof, is D2E7.

12. **(Original)** The method of any one of claims 8, 9, or 10, wherein the TNFα antibody is administered with at least one additional therapeutic agent.

13. **(Original)** A method of treating a subject suffering from a TNFα-related disorder selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis, such that said TNFα-related disorder is treated.

14. **(Original)** The method of claim 13, wherein D2E7 is administered with at least one additional therapeutic agent.

15. **(Currently amended)** A kit comprising:

a) a pharmaceutical composition comprising a TNFα antibody, or an antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody dissociates from human TNFα with a $K_d$ of $1 \times 10^{-8}$ M or less and a $K_{off}$ rate constant of $1 \times 10^{-3}$ $s^{-1}$ or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard *in vitro* L929 assay with an $IC_{50}$ of $1 \times 10^{-7}$ M or less; and

b) instructions for administering to a subject the TNFα antibody pharmaceutical composition for treating a subject who is suffering from a TNFα-related disorder.

16. **(Original)** The kit of claim 15, wherein the TNFα-related disorder selected from the group consisting of Behcet's disease, ankylosing spondylitis, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), restenosis, diabetes, anemia, pain, a Crohn's disease-related disorder, juvenile rheumatoid arthritis (JRA), a hepatitis C virus infection, psoriasis, psoriatic arthritis, and chronic plaque psoriasis.

17. **(Original)** A kit according to claim 16 , wherein the TNFα antibody, or an antigen binding portion thereof, is D2E7.